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10/623,891	07/21/2003	Sanjay M. Reddy	0167.03	6885

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EXAMINER	
MCGAW, MICHAEL M	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,891	REDDY ET AL.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicant's communication filed on September 20, 2004. Claims 4 and 11 have been cancelled. Claims 1, 8, 9 and 15 have been amended. Claims 1-3, 5-10 and 12-15 are currently pending.

Claim Rejections - 35 USC § 112, ¶2

Claims 3, 5, 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new, non-art rejection under 35 USC § 112, ¶2.

These claims are directed to a "Marek's disease virus having ***all of the identifying characteristics*** of strain ATCC PTA-4945." (emphasis added) This is not the same as merely claiming the strain ATCC PTA-4945. Instead, it is broader and would encompass any virus having "all of the identifying characteristics..." whatever those characteristics may be. Applicant has not described the set of characteristics which identify strain ATCC PTA-4945. Consequently, the metes and bounds of that to which applicant is claiming remains undefined and would not adequately inform the public of the bounds of that which applicant regards as his invention.

Claim Rejections - 35 USC § 112

The rejection of claims 3, 5, 10 and 12 under 35 USC § 112, ¶1 made in the Office Action dated June 16, 2004 is withdrawn in view of Applicant's deposit of CVRM-2 with the ATCC under Accession No. ATCC PTA-4945.

Response to Amendment

Claims 8 and 9 have been amended in response to the rejection in the previous Office Action. The rejection of these claims under 35 USC § 112, ¶2 is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 112

1. Claims 3 and 10 were rejected under 35 USC § 112, ¶2 in the previous Office Action as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. This rejection is maintained.

The claims are generally directed to a viral agent; product claims. The claims indicate "said long terminal repeats sequence comprises a *Pac I* excised DNA segment from a Marek's disease virus..." It is the Examiner's understanding that the long terminal repeat sequence is excised from a larger nucleic acid via *Pac I* restriction endonuclease digestion. Thus, one would be left with a linear nucleic acid with the partial *Pac I* palindrome at the extreme ends of the sequence. Paragraph [0055] of the specification indicates that this sequence is inserted into B40-Pac, which is then

digested with *Not I*. It is not clear whether or not the *Not I* excised fragment that is to be recombined still has the *Pac I* site and, more importantly, whether the *Pac I* site is maintained during recombination. This *Not I* digested nucleic acid would then be used to transform a virus via recombination. The sequence that would be integrated would be internal to either extreme end. The point of this is that, as stated in the previous action, the identity of the particular restriction site would appear to be irrelevant since the site would be lost during recombination. The long terminal repeat is not adding/delivering a *Pac I* site to the virus to which it transforms, though this seems to be what the claim is suggesting. The bottom line is that the process by which the LTR was excised does not impart any distinctive structural characteristics to the final product. That a *Pac I* site "would most likely be present in the recipient CVI988 MDV strain (or any other CVI988 strain) [into which the LTR subsequently recombines] because the herpesvirus genome is highly conserved" is a tangential matter and does not resolve the problems of claims 3 and 10 as outlined above.

Claim Rejections - 35 USC § 103

Applicant's arguments filed September 20, 2004 have been fully considered but they are not persuasive.

Claims 1, 2, 5, 6, 9 and 13 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Witter et al. (1997) in view of Witter et al. (1995). Claims 1 and 9 have been amended to import the limitations of claims 4 and 11, while claims 4 and 11 have been cancelled.

Applicant's arguments are based upon the assertion that "a practitioner of ordinary skill in the art would still have no motivation to combine the references as suggested, nor would they have any reasonable expectation of success" based upon the combined teachings of Witter et al. (1997) in view of Witter et al. (1995), or further in view of Jones et al. (1996) in regards to cancelled claims 4 and 11. Applicant has further asserted that Examiner's reasoning is based upon an 'obvious to try' rationale. As stated above, this is not persuasive.

1. No Motivation

First, the combined teachings of Witter et al. (1997) in view of Witter et al. (1995) would motivate one of ordinary skill in the art. In summary, Witter et al (1997) teaches a viral agent comprising recombinant Marek's disease virus (RM1) stably transformed with a foreign DNA construct which comprises a long terminal repeat sequence of reticuloendotheliosis virus, wherein said viral agent is effective to elicit an immune response in a chicken to Marek's disease virus, and further wherein said long terminal repeat sequence is inserted upstream of the ICP4 gene of said Marek's disease virus. Witter et al. (1997) does not teach the strain CVI/988X nor does he teach a viral agent that does not cause a significant degree of pathogenicity, as claimed in claim 1, though the reference does make numerous efficacy comparisons to CVI/988 and substantially recognizes the problem of the pathogenicity of the vaccine. In the second to last sentence, Witter et al (1997) indicates that the principal problem with the use of RM1 as a vaccine was the issue of thymic atrophy (i.e. it caused a significant degree of

pathogenicity). In closing, Witter et al. (1997) states that states that selective mutation [with REV] may be an advantageous strategy for the development of superior serotype 1 MDV vaccines. This is both motivation and a suggestion. The suggestion would be to find a means to overcome the issue of thymic atrophy.

The previous Office Action addressed the details of Witter et al. (1997). The following is an excerpt from the previous Office Action:

> Witter et al (1997) *Avian Diseases*, **41**:407-421 discloses a recombinant MDV, referred to as RM1, based upon the JM/102W strain of MDV, which was stably transformed with the LTR of REV (page 408) (See also Jones et al, *J. Virol.* (1996) p. 2460-67 which describes more fully the creation of RM1). Witter reported that RM1 was effective to elicit an immune response in chickens (page 413) and that the response was highly protective upon challenge (Table 7 on page 418), greatly exceeding that of the attenuated serotype 1 vaccine strains CVI988 and JM/102W (upon which it was based). Witter reports that JM/102W(passage 48), like other attenuated serotype 1 MDVs, replicates poorly *in vivo* (page 418). In contrast, RM1 replicated efficiently *in vivo*. Moreover, RM1, like the attenuated viruses often used in vaccines, did not result in significant oncogenicity (page 416). Witter speculates that the LTR insertion induced the greater *in vivo* replication, which, in turn, resulted in the increased protection in RM1 vaccinated chickens upon challenge with virulent MDV (page 418). Witter points out that RM1 is not a good candidate for commercial vaccine development due to its ability to cause persistent thymic atrophy and residual oncogenicity, but that it does represent a model for future vaccine development (page 420). In particular, Witter provides that the "selective mutation of key genes [with REV] will prove to be a useful strategy for development of superior serotype 1 vaccines." (See last sentence of text on page 420).

Witter also reports that this RM1 strain provided superior protection to the CVI988 strain though the parent strain from which RM1 was derived provided inferior protection, which is relevant to the present application. (See also table 7) Witter reports that the next best vaccine in terms of protective ability to the RM1 strain was CVI988/Rispens vaccine. (pg. 419, column 2) Witter et al. (1997) concludes by pointing out that RM1 is not a likely candidate for commercial vaccine development due to its tendency to cause persistent thymic atrophy. (See second to last sentence of Witter (1997) straddling pgs. 419-420) As noted above, this is a clear suggestion to adopt a

strain with a reduced potential for thymic atrophy. Given the protection shown in Witter et al. (1997) one would be motivated to create similar vaccine constructs using LTR inserted into MDV.

Unlike JM102/W into which Witter et al. (1997) inserted the LTR, Witter et al. (1995) report that CVI988/Rispens does not induce thymic atrophy. Moreover CVI988 was the vaccine strain that Witter et al (1997) reported as second to only RM1 in protective efficacy. Therefore, motivation exists to combine the references.

2. No Reasonable Expectation of Success

Second, one would have a reasonable expectation of success. The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986)

The techniques involved in creating a recombinant MDV vaccine harboring the LTR of REV were well established at the time of applicant's invention and these techniques are taught in a number of the references cited by Applicant including Witter

et al. (1997). Therefore one would have a reasonable expectation of success in making the viral agent claimed by applicant. As noted above, this does not require absolute predictability. Applicant has not provided evidence that shows that, at the time of applicant's invention, there would be no reasonable expectation of success. Applicant has submitted Parcells et al (2004).

Applicant points to the Parcells et al (2004) abstract as evidence that one would have no reasonable expectation of success in creating the claimed invention as suggested by the combining of the two Witter references. This appears erroneous for a number of reasons. First, reasonable expectation of success must be determined at the time of Applicant's invention. As for the Parcells et al abstract, this post-dates Applicant's invention by at least one year. One skilled in the art could not be daunted by unknown obstacles although the subsequent publications might be relevant to show that the obstacles actually applied to the specific problems facing the inventor. Velander v. Garner, 68 USPQ2d 1769, 1783 (CA FC 2003)

Second, Applicant has suggested that Parcells represents failure because the resulting transformants containing the inserted LTRs did not exhibit enhanced replication. However, enhanced replication is not a claimed feature of Applicant's invention. Consequently, it appears at first blush that Parcells succeeded in doing exactly what Applicant is claiming, though they may have failed in that the insert was downstream of the ICP4 gene? If so, this might further explain the reduced replication relative to Witter et al (1997).

Finally, that Parcells attempted to do what is taught by the combined Witter references, and Applicant's invention, seems to bolster the notion that one would be motivated to do this and have a reasonable expectation of success in so doing. Otherwise Parcells would not have attempted it. It is noted that the Witter et al. (1997) publication has authors who are also inventors on the present application. It has been outlined above how Witter et al. (1997) in view of Witter et al. (1995) provides the motivation and suggestion in support of the present rejection. (See especially final line of Witter et al (1997)). It is noted that Applicants assert that one would have no reasonable expectation of success based on the statements in Witter et al. (1997). This is not found persuasive.

3. Obvious to Try

As a final matter, Applicant has asserted that the Examiner's rejection was based merely on an "obvious to try" rationale. As provided in *In re Merck & Co., Inc.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986):

> "[O]bvious to try is not the standard of 35 U.S.C. § 103." *In re Antonie,* 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977) (emphasis omitted). Rather, the test is whether the references, taken as a whole, would have suggested appellant's invention to one of ordinary skill in the medicinal chemical arts at the time the invention was made. *In re Simon,* 461 F.2d 1387, 1390, 174 USPQ 114, 116 (CCPA 1972). Obviousness does not require absolute predictability. *In re Lamberti,* 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976). Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness. *In re Longi,* 759 F.2d 887, 897, 225 USPQ 645, 651 (Fed. Cir. 1985).

Applicant is correct to the extent that obvious to try is not the proper standard. Nevertheless, the rejection was based on more than merely an obvious to try rationale. As outlined above, one would have had a reasonable expectation that a beneficial result

would be achieved. Moreover, the obvious to try rationale is not on point in the present instance. The following is an excerpt from MPEP 2145:

> "The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)

No suggestion was made in to vary a multitude of parameters nor was the suggestion one of the exploration of new technology or general approaches. Instead, the motivation and suggestion was quite specific. Therefore, Applicant's arguments are not found persuasive.

Limitation Added by Amendment to Claims 1 and 9 - Rejection under 35 USC § 103

Claims 4 and 11 were rejected under 35 U.S.C. 103(a) as being unpatentable over Witter et al (1997) over Witter et al (1995) as applied to claims 1 and 9 above, and further in view of Jones et al (1996). The limitations of claims 4 and 11 were imported into claims 1 and 9, and claims 4 and 11 were then canceled. In the interest of clarity these limitations are being dealt with separately.

Jones et al provides the details of the MDV RM1 vaccine virus used by Witter et al (1997) and is explicitly referenced by Witter throughout page 408. In particular, Jones teaches that the insertion of the LTR is in the vicinity of the MDV ICP4 gene (see pg. 2466; col.1; last full sentence). Jones states, "Since a potential promoter for the long form of the MDV ICP4 gene is located 100 to 200 bp upstream from the LTR insertion

site, it is conceivable that the ICP4 transactivator may also be associated with the novel phenotype of RM1." The quote is relevant for two reasons. First, where the promoter for ICP4 is upstream of the LTR, it is reasonable to conclude that the insertion of the LTR was in between the ICP4 promoter and the ICP4 gene, which would place the LTR upstream of the ICP4 gene upstream as specified in amended claims 1 and 9. This conclusion is bolstered by the observation in Jones et al. that integration patterns are clustered and region-specific. (See pg. 2465, column 1) Second, Jones et al correlates the desired phenotypic change with the locality of the insertion of the LTR. As an academic matter, given that Witter et al (1997) references Jones et al for support on construction of RM1, all of the limitations are properly attributable to Witter in view of Witter without resort to Jones except for explanation.

Applicants indicate on page 11 (final line) that the increased rate of replication is the result of the insertion of the reticuloendotheliosis virus LTR into the genome of the Marek's disease virus upstream of the ICP4 gene. Further, it is stated, "This is not disclosed or suggested in the prior art." In fact, this appears to be exactly the thing that is taught in the suggested in Jones et al./ Witter et al (1997) sequence of papers dealing with the RM1 strain containing the LTR.

Applicant's state on page 14, "It is only by virtue of Applicants' invention that the point of insertion can be controlled and LTRs can be introduced into other Marek's disease viruses to produce effective vaccine." It is the Examiner's understanding that the LTR enters the MDV genome by homologous recombination. As mentioned above, Jones et al. teaches that integration patterns are clustered and region specific. (See

also Jones et al. PNAS (1993) cited by applicant as AT1) It is not evident how Applicant's invention controls the point of insertion to any greater extent than that seen in Jones et al. (1995) Unlike the addition of a nucleic acid sequence via restriction digest and ligation, homologous recombination is somewhat random.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 8, 12, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Witter et al (1997) over Witter et al (1995) as applied to claims 1, 2, 5, 6, 9, and 13 in the previous Office Action dated June 16, 2004 and elaborated in the present action.

Claims 3, 8, 10 and 12 were rejected in the previous Office Action dated June 16, 2004 under 35 USC § 112. The rejection under § 112 as to claims 3 and 10 has been maintained in the instant Office Action. Applicant is correct in pointing out that claims 14 and 15 were not specifically mentioned in the Office Action of June 16, 2004. This oversight was unintentional on the part of the Examiner. However, all of the issues raised/limitations found in these claims were dealt with previously. Claim 14, like claim 7, concerns the cell-associated nature of the virus vaccine. The cell-associated nature of the virus was discussed in the final paragraph on page 7 of the previous Office Action

dated June 16, 2004. Claim 15 claims a "method for making a viral agent effective for protecting a chicken against Marek's disease comprising transforming a Marek's disease virus strain CVI988 with a foreign DNA construct which comprises a long terminal repeat sequence of a reticuloendotheliosis virus." This claim stands rejected under the art of record; Witter et al (1997) over Witter et al (1995) as applied to claims 1, 2, 5, 6, 9, and 13 the previous Office Action dated June 16, 2004. All of the limitations found in the claim were addressed in that Office Action.

Conclusion

Claims 1-3, 5-10 and 12-15 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571)

272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M.M.

Wednesday, November 17, 2004

JAMES HOUSEL 11/29/04
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